Statistical Hypothesis Testing

Helena Chmura Kraemer

Stanford University

Recapitulation

- Have a theory.
- Sampling, Design, measurement, treatment protocols.
- Need to set rule as to what evidence from the RCT would lead to recommendation for T over C.
  - Most common current method: Null Hypothesis Statistical Testing (NHST).
  - Greater Emphasis in Future (?): Effect sizes.

The Overuse, Misuse, Abuse of NHST

- Should NHST be "outlawed"?
- Signs of abuse:
  - Tables and text full of ***, NS, p-values
  - "Statistical significance" interpreted as big, important, useful (when it may be trivial)
  - "Non statistical significance" interpreted as "proof" of the equivalence (when it indicates poor

Analogy: Trial by Jury vs. NHST

- Trial by Jury
  - You: The Prosecutor
  - Evaluation of Evidence: Judge/Jury
- NHST
  - You: The investigator
  - Evaluation of Evidence: Other scientists, reviewers, editors, readers, clinicians, policy makers, medical consumers or advocates.
  - Biostatisticians: The gadflies? The lawyers?

Exploratory Phase

- Gather evidence, testimony, etc. until have enough to bring charges, indict.
- Theory, Animal Studies, Clinical Observation, Pilot Studies, Phase I, II studies, until have rationale and justification for your theory than T is better than (different from) C.

Hypothesis Specification

- Charges are few and specific. Some may be dropped during the trial, but none added during the trial in response to evidence.
- Hypotheses are few and specific. Some may be dropped during the RCT, but none added “post hoc”.

Preparing for the Trial

- Assemble the judge, jury to hear the evidence and render the verdict. Instructions to the jury to prevent mistrial.
- Design the RCT to generate evidence needed to adequately and fairly test theory. Set the rule that will support your theory “a priori”. Submit the proposal for review.
  - IRB
  - Peer review group

Objectivity

- The defendant is presumed innocent until proven beyond reasonable doubt to be guilty of stated charges.
- The "null hypothesis", i.e. the denial of your theory, is presumed true until you prove beyond reasonable doubt that it is false.
  - "Beyond reasonable doubt" means that the probability of claiming that your theory is true when it is not (null hypothesis true) is less than an a priori set significance level (usually 5% or 1%).

Interpretation of the Verdict–1

- "Guilty" means evidence was sufficient to prove guilt of stated charges beyond reasonable doubt.
  - May appeal the verdict.
- "Not guilty" means evidence was not sufficient to prove guilt of stated charges beyond reasonable doubt.
  - No double jeopardy

Interpretation of the Verdict–2

- "Statistically significant" means evidence was sufficient to prove beyond reasonable doubt (5% or 1%) that the null hypothesis is not true, and hence provides support for your theory.
  - Replication and independent confirmation always required. Meta Analysis?
  - Does not mean "large" or "important". It may not indicate clinical or policy significance.
- "Not statistically significant" means your evidence was not sufficient: inadequate power.
  - Learn from your mistakes!

Caveats:
The Burden of Proof is on You

- Don’t initiate trial until preliminary evidence is strong enough.
  - Present the evidence competently.
- Don’t initiate RCT without sufficient rationale and justification
  - Valid sampling, design, analytic procedure
  - Reliable and valid outcome, and few of them.
  - High enough power.
  - Stick to your own protocol!
  - Don’t over generalize or exaggerate your results.

Example-1

- Theory: T>C
- Treatment, design and measurement protocols
  - Sample N patients
  - Randomly assign proportion P to T. P'=1-P to C.
  - Measure response to treatment with bias controlled.
- Analytic plan:
  - Compare T versus C, and if response to T is sufficiently better than that to C, reject the null hypothesis (here that T<C, one-tailed)

Example-2: Specifically how?

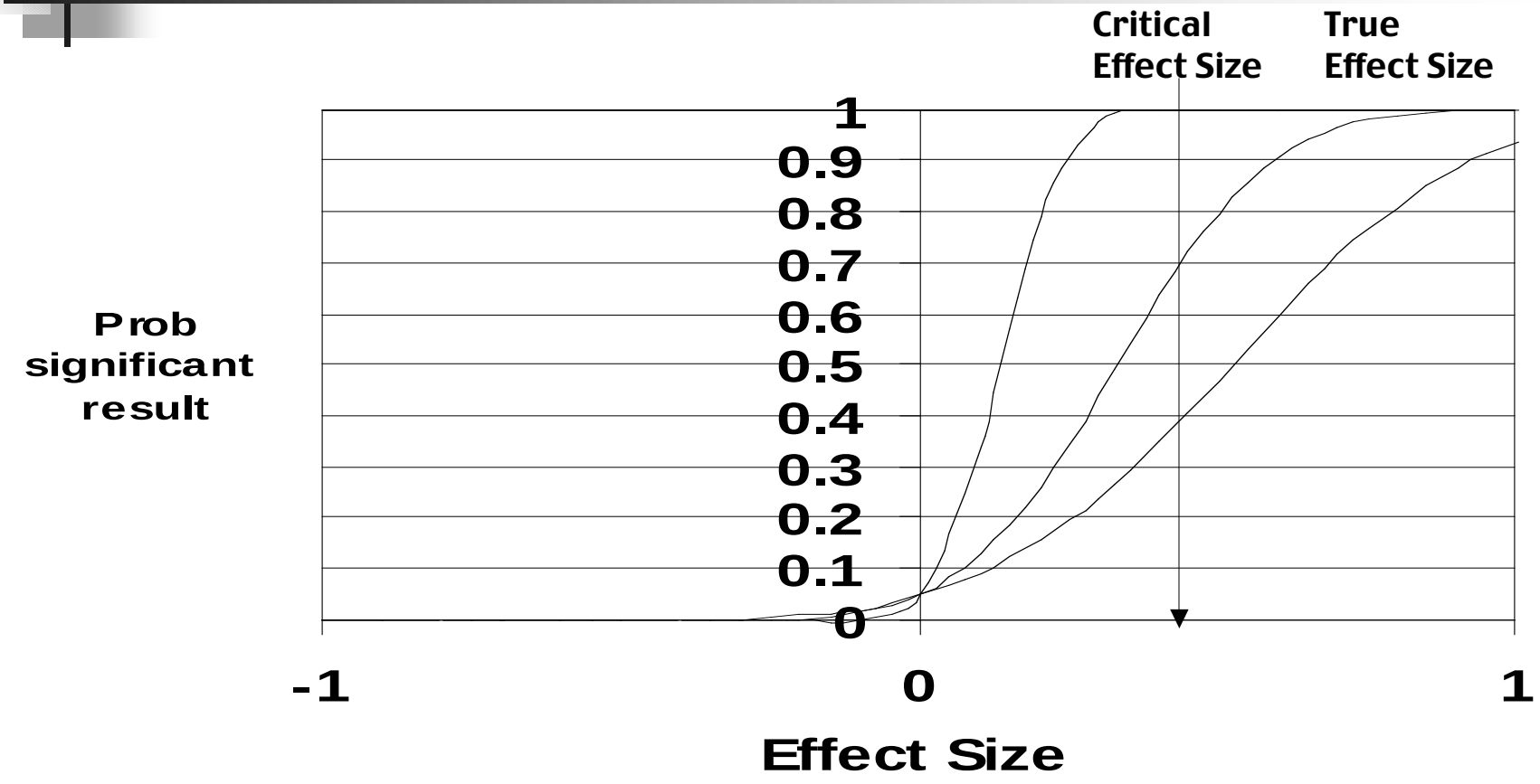
Student's t-test: Compute t-statistic, and compute the p-value: a statistic estimating the probability of rejecting null hypothesis when the effect size is that observed. If p-value <5%, the reject null hypothesis (declare statistically significant at the 5% level).

Mann-Whitney Wilcoxon: Compute the test statistic and compute the p-value etc.

2X2 Chi Square test: Compute the success rate in T and compare with that in C. Compute the test statistic and compute the p-value, etc.

Correlation Test: Compute the correlation coefficient between outcome and exposure to

Example–3: What is N? P? Will I have enough power?



Example-4: Where do mistakes happen with power?

- Critical effect size set at heart's desire rather than threshold of clinical significance.
- Simple miscalculation.
  - Proposing to do Chi-Square test, but computing power using t-test.
  - Making assumptions unlikely to be true.
    - Assuming normal distributions, equal variance when that is not true.
    - Assuming absence of site differences in a multi-site study.

The Problem of Effect Size

- Common choices (Rules of Thumb):
  - T-test: Cohen's d, the standardized mean different between the treatment means. (Null: d=0; Small: .2; Medium: .5; Large: .8.)
  - Mann-Whitney-Wilcoxon: AUC=Prob(T>C)+.5Prob(T=C). (Null: 50%; Small: 56%; Medium: 64%; Large: 71%.)
  - 2X2 Chi-Square: Odds Ratio, Risk Ratio, Risk Difference.
    - AUC=.5(1+RD)
  - Correlation Coefficient: (Null: 0; Small: .1; Medium: .3; Large: .5.)
- To date, largely based on statistical, not clinical or policy considerations.

And when the RCT is done?

- Write up the results, and celebrate!
- Learn from your mistakes.
- Formulate new hypotheses for future testing
  - Moderators of treatment: Factors measured at baseline that identify on whom or under what conditions the treatment works better or worse.
    - Why important? Selection for treatment; Inclusion/exclusion criteria, stratification for future studies.
  - Mediators of treatment: Events or changes during treatment that may help explain how or why the treatment works.
    - Why important? Suggestions for improvement of treatment efficacy or effectiveness.

Conclusion

- If use NHST, always present effect sizes for any statistically significant result, and some measure of the accuracy of estimation.
- If don't use NHST, consider using effect sizes and some measure of the accuracy of estimation. Possibly Bayes' estimation?
- Statistical significance is necessary, but not sufficient! Ultimately the crucial issue is the benefit to the patients, i.e. clinical or policy significance.